Executive Highlights

Hello from FDA headquarters in Silver Spring, MD, where the FDA's Endocrinologic and Metabolic Drugs Advisory Committee meeting on a potential label update for Novo Nordisk's GLP-1 agonist Victoza (liraglutide) has drawn to a close. On the committee's agenda was the question of whether an additional indication should be added to the Victoza label for the reduction of the risk of cardiovascular events on the basis of the LEADER trial results, presented last year at ADA 2016. The meeting was filled with twists and turns - see below for our top highlights from this thought-provoking event, as well as our coverage of the Open Public Hearing and each panelists' rationale for their voting decision.

Top Six Highlights

1. The Advisory Committee ultimately overwhelmingly voted 17-2 in favor of an additional indication of reduction in cardiovascular risk for Novo Nordisk's Victoza (liraglutide) based on the findings of the LEADER trial. As expected, the panel rendered a unanimous "yes" verdict on the first question asking whether the trial had successfully established cardiovascular safety. Although numerically decisive, the advisory committee's apparent consensus on the question of a cardiovascular indication for Victoza was murkier than the vote count would suggest; the "yes" voters almost universally expressed some concerns.

2. Over and over, panelists highlighted the impressive and convincing consistency of CV results in LEADER, from the primary three-point MACE endpoint (non-fatal MI, non-fatal stroke, and CV death) to each individual component of the MACE endpoint to the reduction in all-cause mortality. The issue of whether the single LEADER trial could support approval of a new efficacy indication was raised several times, and the consistency of CV endpoint findings were ultimately reassuring on this front. Each time a panelist wondered if another confirmatory trial could be done, we groaned a little internally. This is one element of 2008 guidance that seems a mismatch with what is reasonable to ask manufacturers to take on.

3. A notable point of contention during the committee's discussion and vote on cardiovascular risk reduction was how broad the indication should be, particularly in terms of the target patient population. A majority of voting members expressed that Victoza's new indication should only apply to type 2 diabetes patients at highest-risk for CV events - an opinion based primarily on a subgroup analysis that showed a hazard ratio for three-point MACE of 0.83 in favor of liraglutide for a high-risk cohort (95% CI: 0.74-0.93) vs. 1.2 in favor of placebo for a slightly lower-risk cohort (95% CI: 0.66-1.67).

4. At the crux of much of the day's debate were concerns over the lack of a statistically significant cardiovascular benefit for Victoza in the US subgroup of the LEADER trial. This was a key area of concern for the FDA and for several panelists, many of whom felt that this anomalous result in this subgroup calls the generalizability of the overall LEADER findings into question for patients living in the United States.

5. The most interesting theme to emerge from discussion of LEADER safety data was that several voting members advocated for the removal of Victoza's black box warning for medullary thyroid cancer (MTC). Opinions diverged somewhat on neoplasms and pancreatitis, but the consensus remained that none of these items warrants real concern, and that all are far outweighed by the compelling CV data.

6. 13 clinicians, patients, and public health advocates spoke during the Open Public Hearing portion of the day. Of these, 11 speakers (encompassing a broad range of diabetes healthcare providers, leaders of professional organizations, patient advocates, and patients to speak during the public hearing portion) offered strong endorsements in favor of approval of the updated indication.

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Top Six Highlights

1. Advisory Committee Votes 17-2 in Favor of a CV Indication for Victoza

The Advisory Committee ultimately overwhelmingly voted 17-2 in favor of an additional indication of reduction in cardiovascular risk for Novo Nordisk's Victoza (liraglutide) based on the findings of the LEADER trial. As expected, the panel rendered a unanimous "yes" verdict on the first voting question of whether the trial had successfully established cardiovascular safety, as per the 2008 FDA Guidance requiring new diabetes drugs to rule out an "unacceptable" additional CV risk of 30% compared to placebo as a post-marketing requirement. Although numerically decisive, the advisory committee's apparent consensus on the question of a cardiovascular efficacy indication for Victoza was murkier than the vote count would suggest (and indeed, than we initially expected given the less contentious tone we detected in the FDA's briefing document released late last week). While panelists agreed that the cardiovascular outcomes were impressive and potentially enormously meaningful for patients and population health more broadly, virtually every panelist who voted "yes" expressed some concerns. Chief among them were the difficulty of disentangling whether Victoza's cardioprotective effects extend beyond secondary prevention to also support primary prevention, the lack of a statistically significant risk reduction with Victoza for every single individual cardiovascular outcome measured, a reticence to base label updates on a single trial, and the lack of a significant cardioprotective benefit in the subgroup of US participants to mirror that seen in the overall analysis. This issue of the worse point estimate for hazard ratio in the US subgroup was particularly contentious during the panel's discussion, and was cited as the main rationale for both of the "no" votes (much more on each panelist's individual rationale in the Detailed Discussion and Commentary section below). That said, many of the panelists ultimately found the US subgroup to be less of an issue when examining the totality of results - the subgroup analysis based on baseline CV risk gained more traction, on the other hand (more on both of these issues below). All in all, the FDA is in an interesting position going forward. While we expect a label update based on the positive vote (and the precedent set by Jardiance's label update on the basis of similar data), we would not be surprised if the FDA opts for a more conservative indication than the sweeping one Novo Nordisk originally submitted for. Specifically, the company's briefing document stipulates the requested additional indication for Victoza "as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (CV death, non-fatal MI, or non-fatal stroke) in adults with type 2 diabetes and high CV risk" but it is quite possible that the FDA will instead propose a narrower indication that more tightly specifies who is considered to be at "high CV risk" to

more accurately reflect the higher risk portion of the LEADER study population that appeared to drive the majority of the CV benefit.

- **To us, the many concerns and qualifications that accompanied this majority of "yes" votes illustrates the sheer complexity of clinical trial design and statistical analysis, rather than any doubt about the robustness of the LEADER trial itself (which many panelists went out of their way to praise for its impeccable execution).** Despite a seemingly endless number of ways the LEADER data could be cut, some unresolved ambiguities on this front - in this case subgroup analyses of participants in US versus non-US geographies and participants in the primary versus secondary prevention cohorts - are unanswerable and must boil down to individual judgement calls. For comparison, despite the concerns raised even by the majority of "yes" voters, we view Victoza's Advisory Committee Meeting as decidedly less contentious than the corresponding EMDAC meeting last June for a cardiovascular indication for Lilly's Jardiance (empagliflozin), which ended in a razor-thin 12-11 vote in favor of a cardiovascular label update on the basis of the EMPA-REG OUTCOME results. More on this voting decision here.

2. Compelling Consistency of CV Benefit in LEADER Trial and Comparisons to EMPA-REG OUTCOME

Over and over, panelists highlighted the impressive and convincing consistency of CV results in LEADER, from the primary three-point MACE endpoint (non-fatal MI, non-fatal stroke, and CV death) to each individual component of the MACE endpoint to the reduction in all-cause mortality. Committee members expressed that the consistency of the CV results was a key factor lending confidence to the validity of the CV benefit of liraglutide. As Dr. David Oakes put it, "All of the components move in lockstep." Dr. James Neaton also emphasized the fact that all of the components of the MACE endpoint support the primary endpoint finding and the very compelling CV and all-cause mortality reductions. This consistency was particularly notable in comparison to the Advisory Committee discussion for the proposed CV indication for Jardiance a year ago. Last year, the heterogeneity in the point estimates for individual components of MACE, and the fact that Lilly/BI were seeking an indication specifically for the secondary endpoint of standalone CV death, were sticking points that led to a very close 12-11 vote. Indeed, several members of today's Advisory Committee were part of the discussion for the Jardiance indication and made explicit references and comparisons to last year's meeting in today's discussion. In particular, the great Dr. Judith Fradkin, from NIDDK, compared the LEADER findings favorably to the EMPA-REG OUTCOME findings, emphasizing the consistent trend for benefit with positive point estimates for all three components of MACE.

- **The issue of whether the single LEADER trial could support approval of a new efficacy indication was raised several times, and the consistency of CV endpoint findings were ultimately reassuring on this front.** Each time a panelist wondered if another confirmatory trial could be done, we groaned a little internally. This is one element of 2008 guidance that seems a mismatch with what is reasonable to ask manufacturers to take on. Dr. Daniel Budnitz reiterated that the FDA considers three criteria to support a single-trial approval: (i) similar benefit demonstrated in a pharmacologically similar drug; (ii) biomarker evidence supporting the data; and (iii) statistically convincing evidence. In his view, the LEADER trial did not meet the first two criteria, so the main consideration at hand is whether or not the findings can be considered statistically convincing. (That said, Dr. Fradkin pointed out that the SUSTAIN 6 trial of Novo Nordisk's semaglutide offers some substantiating evidence of CV benefit in a pharmacologically similar drug.) Dr. Marvin Konstam was certainly convinced by the LEADER data from a statistical perspective, citing the low p-value, large number of events, consistency of MACE components, and consistency with prior data from phase 3 trials. Dr. James de Lemos was more reserved in his judgement, and he actually characterized the MACE p-value as borderline in terms of whether the single trial constitutes sufficient evidence for approval (based on his experience with cardiovascular drug trials). That said, he posited that the bar for the approval of an expanded indication to an

already-marketed drug may be different and he suggested that the consistency in CV death and MACE findings together offer confidence for approval.

- **As could be expected, several comparisons to EMPA-REG OUTCOME arose in the discussion period.** Dr. Fradkin found the Kaplan-Meier curves for CV events in LEADER suggested benefit on atherosclerosis progression, with their gradual and steady separation throughout the trial - this contrasts with the earlier and steeper divergence observed in EMPA-REG OUTCOME. Furthermore, several panelists pointed out that the p-value for superiority for the primary endpoint was much more compelling in LEADER than in EMPA-REG OUTCOME (p=0.01 vs. p=0.038) - the "barely significant" p-value in EMPA-REG OUTCOME was a major point of concern for some committee members last year.

3. Cardioprotection in Which Population?

A notable point of contention during the committee's discussion and vote on cardiovascular risk reduction was how broad the indication should be, particularly in terms of the target patient population. A majority of voting members expressed that Victoza's new indication should only apply to type 2 diabetes patients at highest-risk for CV events. This opinion was based primarily on a subgroup analysis of higher-risk (3a) vs. lower-risk (3b) participants in LEADER. In the 3a cohort, all participants were ≥50 years-old with type 2 diabetes and established cardiovascular or renal disease at baseline (history of MI, stroke, peripheral vascular disease, or class II-III heart failure, arterial stenosis >50% or symptomatic/asymptomatic ischemia, and eGFR <60 ml/min/1.73m^2). Notably, however, this cohort is somewhat more inclusive than the typical "secondary prevention" definition of previous history of CV events. In the 3b cohort, type 2 diabetes patients were ≥60 years-old and presented with several CV risk factors at baseline (microalbuminuria/proteinuria, hypertension/left ventricular hypertrophy, left ventricular dysfunction, and an ankle brachial index <0.9). For the primary outcome of three-point MACE, the subgroup analysis found a hazard ratio point estimate of 0.83 in favor of liraglutide for 3a (95% CI: 0.74-0.93) vs. 1.2 in favor of placebo for 3b (95% CI: 0.66-1.67). While this latter hazard ratio trends in the wrong direction, the confidence interval crosses the line of unity, so this finding does not reach statistical significance. Moreover, Dr. Moses pointed out that the sample size gets too small in subgroup 3b to yield any meaningful CV finding (n=1,742, with 7.9% of this lower-risk cohort experiencing a MACE event). Even so, the dominant opinion from the Advisory Committee voting panel was that liraglutide has only demonstrated cardioprotection among people facing very high CV risk, and we imagine this could sway the FDA's decision on the exact language of an indication. Novo Nordisk's requested CV indication would extend to patients with type 2 diabetes and "high cardiovascular risk," but it seems plausible that the FDA would amend this to "established cardiovascular disease" or some other more stringent language before approving a label change - this would be similar to the indicated CV population for Jardiance, though the Jardiance CV approval was based on a trial that only enrolled patients with established CV disease. While it's true that LEADER enrolled a rather high-risk participant pool, Dr. Michael Blaha underscored during his voting rationale that diabetes is a major CV risk factor in itself and that the entire type 2 diabetes patient population is at a substantially elevated risk for CV morbidity/mortality as is (absolutely true). So yes, diabetes drugs would ideally show signals for primary CV prevention, but considering how many accrued MACE events it takes to power a CVOT and draw compelling conclusions of superiority, we do understand Novo Nordisk's enrichment strategy of enrolling high-risk patients. We don't quite share the concern of some other voting members that approving an indication too broad would be particularly harmful, given that liraglutide is already on the market as Victoza and as Saxenda (for obesity) and is prescribed to people across the spectrum of CV risk factors. We also maintain that any new CV indication added to the product label, even if shrunken in scope, could do a world of good - it would raise awareness among diabetes patients that they face heightened risk for CV events, and it would arm diabetes providers with another potential cardioprotective tool.

- **This discussion also pushed the Advisory Committee to confront the heterogeneity of diabetes, a topic that isn't talked about enough, especially at the regulatory level.** As Dr. Cecilia Low Wang articulated during her voting rationale, the confusion over liraglutide's differential CV effects in highest-risk vs. high-risk participants, in type 2 diabetes patients with and without chronic kidney disease, in patients residing in the US vs. ex-US, etc. all highlights the heterogeneity

of type 2 diabetes. "We should keep that in mind as we're thinking about drug labels," she affirmed. We'd certainly love for FDA to give greater consideration to the extremely varied patient experiences with diabetes, as this diversity of experience is part of what necessitates a wide range of effective therapies. Dr. Low Wang suggested that the next trial (if there were to be one) should look at primary prevention of atherosclerotic CV disease. Thought leaders in the field have echoed this sentiment, hinting that the next big step for diabetes drugs is to show CV efficacy from an earlier stage, before people have their first MACE event (now that EMPA-REG OUTCOME and LEADER have convincingly showed that certain diabetes drugs can prevent further CV complications in patients at high-risk). Of course we'd be thrilled to see a primary prevention study, but again, we recognize the immense time and massive amount of resources that go into conducting each and every CVOT.

4. Concerns Regarding Lack of Statistically Significant Cardiovascular Benefit in the US Subgroup

At the crux of much of the day's debate were concerns over the lack of a statistically significant cardiovascular benefit for Victoza in the US subgroup of the LEADER trial. As revealed in the FDA's presentation, the hazard ratio for LEADER's primary outcome of three-point MACE was 1.03 (95% CI: 0.84-1.25) for participants living in the US (27% of the overall study population), suggesting a possibility of no cardiovascular risk reduction for Victoza. By contrast, the hazard ratio for this primary outcome for participants living outside the US was 0.81 (95% CI: 0.71-0.92), indicating a 9% risk reduction in cardiovascular events with Victoza in this subgroup. This distinction between US and non-US participants in the LEADER trial was further corroborated in a recent NEJM editorial. This was a key area of concern for the FDA and for several panelists, many of whom expressed concern that this anomalous result in this subgroup calls the generalizability of the overall LEADER findings into question for patients living in the United States. According to the FDA's analysis, this difference in treatment response within the US subgroup could not be explained by the influence of A1c, body weight, or systolic blood pressure, raising the broader question of what could be driving this anomalous result. Dr. Alan Moses, Novo Nordisk's Global Chief Medical Officer pointed out that this may be an issue of lower drug exposure in this subgroup, pointing to data demonstrating a vastly lower number of days of exposure to liraglutide in the lowest quartile of drug exposure in North America (US and Canada) as compared to the LEADER trial's other pre-specified geographies - Europe, Asia, and Rest of World. This reduced drug exposure is presumably due in part to higher rates of treatment discontinuation in the United States - a hypothesis that Dr. Moses supported with an additional findings showing stark drop-off rates in North America versus all other geographies. "This may not completely explain the overall results in this subgroup, but it provides us with confidence that drug exposure is a very important element," he surmised. In fact, this pattern of disproportionate treatment is typical of the US relative to other countries across various clinical trials and is not liraglutide-specific, raising broader questions about adherence, access, and underlying clinical practice in the US. We certainly found this unsettling.

- **In response to these concerns, Novo Nordisk called upon highly respected biostatician Dr. Janet Wittes (President, Statistics Collaborative, Washington, DC) who advised the panel that overall results are more trustworthy in principle than in subgroup analyses.** She described subgroup analyses as "treacherous" and ultimately unreliable on statistical terms, underscoring that subgroup analyses are often impossible to replicate. As a statistician she recommends focusing primarily on the overall results (in this case, participants from all geographies together rather than US versus non-US subgroups), which are much more likely to be "real" rather than the effect of chance. To further underscore this point, Dr. Wittes directed panelists to her recent co-authored NEJM article delving into the interpretation of geographic variation in randomized, controlled trials.
- **FDA statistician Dr. Sue-Jane Wang also responded to the flurry of commentary on these anomalous effects in the US subgroup, advising the panel to keep in mind that the differences here are quantitative but not qualitative.** While the p-value for interaction for the primary endpoint between the US and non-US subgroups was very marginally significant (p=0.048), this does not necessarily signal a qualitative difference in the results by these subgroups.

At best, we can say that there is some difference in the hazard ratio between the US and non-US populations, though it's difficult to say where the "true" hazard ratio lies in the non-US population since the confidence intervals are wide and encompass the overall population primary endpoint point estimate, crossing the line of unity. Given the large overlap in confidence interval between the US and non-US subgroups, it's difficult to state that there is a qualitative difference between the US and non-US CV impact. All in all, it's quite possible that the US finding may be a statistical fluke, given the small sub-population and wide confidence interval.

5. Safety Discussion Considers Cancer, Pancreatitis

The most interesting theme to emerge from discussion of LEADER safety data was that several voting members advocated for the removal of Victoza's black box warning for medullary thyroid cancer (MTC). This black box warning originally came from rodent models that linked liraglutide causally to thyroid c-cell tumors. However, there was only one MTC in the LEADER study, and it presented in the placebo group. The great Dr. Judith Fradkin argued that this black box warning is doing more harm than good: "We're telling people this drug may cause cancer based on animal studies, and that may put off its use by people who could benefit - we should think about the negative effect this language could have on use." She emphasized that LEADER offers a very large dataset, and that the MTC number pales in comparison to the number of CV events. Dr. Hanna Sanoff - one of only two oncologists on the panel - agreed, arguing that we don't have adequate human data on MTC to truly justify the black box warning, that the animal data "aren't really all that relevant right now," and that "we all feel the CV risk reduction outweighs the MTC." This underscores an important point about the power of drug labels, which at the end of the day, is why a new indication would be so impactful (and why we all tune in to these meetings). Label claims, whether positive or negative, do manifest in prescription habits and patient use of these therapeutic agents. While this particular Advisory Committee was not convened to discuss the MTC black box warning, we do hope Dr. Fradkin's and Dr. Sanoff's comments were heard with open ears. A registry of all approved long-acting GLP-1 agonists is ongoing, so incident cases of MTC will be caught and recorded. Perhaps this will provide more evidence to support removal of the black box warning as well.

- **Opinions diverged somewhat on neoplasms and pancreatitis, but the consensus remained that none of these items warrants real concern, and that all are far outweighed by the compelling CV data.** Questions surrounding liraglutide and breast cancer risk arose during the Advisory Committee meeting for Novo Nordisk's Saxenda (liraglutide 3.0 mg for obesity), but malignant breast neoplasms were balanced in LEADER (21 in the liraglutide arm vs. 20 in the placebo arm). There was a slight imbalance in malignant pancreatic neoplasms: In the liraglutide group, nine were adjudicated as definite vs. three in the placebo group. That said, the FDA's presentation acknowledged that the event rate for pancreatic cancer was much too low to make any conclusions (i.e. the risk could be attributable to liraglutide, to other confounding factors, or to chance). On pancreatitis, the FDA presentation called attention to the fact that a greater number of pancreatitis events from the liraglutide group (compared to the placebo group) were not confirmed by the adjudication committee, even though the final numbers were fairly balanced (18 vs. 23 cases for liraglutide and placebo, respectively). The suggestion here is that we shouldn't completely dismiss pancreatitis concerns based on LEADER results alone. On the other hand, a joint FDA/EMA statement in 2014 reported no causal relationship between incretin-based drugs and pancreatitis, despite swirling controversy at the time. Indeed, even the infamous Dr. Peter Butler has largely put the pancreatitis controversy to bed and advocated for the use of GLP-1 agonists as second-line therapy in light of their CV benefit. In digesting all this safety data, some voting members were highly reassured - oncologist Dr. Carmen Allegra pointed out that most diagnoses of pancreatic cancer in LEADER occurred in the first 1.5 years post-randomization, whereas most known cancer-causing agents require at least a decade of exposure, suggesting any carcinogenic exposure occurred before the start of the LEADER trial. Others, including Dr. Kenneth Burman, argued that the median follow-up of 3.5 years in LEADER may not have been long enough to capture the appearance of tumors.

6. Open Public Hearing Features Clinicians, Patient Advocates, and Patients

13 clinicians, patients, and public health advocates spoke during the Open Public Hearing portion of the day. Of these, 11 speakers (encompassing a broad range of diabetes healthcare providers, leaders of professional organizations, patient advocates, and patients to speak during the public hearing portion) offered strong endorsements in favor of approval of the updated indication. Full details on their comments are below. Several speakers highlighted the groundbreaking and clinically meaningful CV benefit and the impact of the knowledge of such a benefit can have on patients, providers, and the larger healthcare system. Additionally - while not explicitly the subject of this Advisory Committee meeting, several speakers touched on the substantial benefits of liraglutide on outcomes beyond A1c, including weight loss and hypoglycemia reduction. On the other hand, two speakers from public health think tanks argued for caution in approving a CV indication for LEADER, emphasizing the signal for increased risk in the US subgroup in the population - this issue was discussed extensively by the committee both before and after the Open Public Hearing portion of the day. Our very own Ms. Kelly Close opened the Public Hearing with a broad perspective on the positive impact of a label indication, while our own Ms. Abigail Dove, Helen Gao, and Payal Marathe closed the public remarks with speeches highlighting the implications of a label update for patient optimism, provider clinical decision-making, the diabetes community. See below for detailed summaries of all speakers' remarks; we also have made public full transcripts of the speeches from Ms. Close, Ms. Dove, Ms. Gao, and Ms. Marathe.

Detailed Discussion and Commentary

Open Public Hearing

- **Representing The diaTribe Foundation, our very own Ms. Kelly Close took a step back to offer a broad perspective on the impact of a CV indication for Victoza, particularly in terms of decreasing CV risk at the population level.** Big picture: the LEADER results are a huge deal - the type of findings that led Ms. Close to wake up her entire family in excitement when the topline results were announced. While giving the FDA credit for bringing advanced therapies like GLP-1 agonists to market, Ms. Close asked that Advisory Committee members and the agency also keep in mind the enormous CV burden of diabetes as well. She emphasized the role the FDA has in helping researchers, clinicians, and patients within the diabetes community get on the same page about new advances in diabetes care. To that end, she emphasized the importance of effectively translating new research - which drug labels can play an important role in. By expanding the label of Victoza to include an indication for reduction of CV risk, Ms. Close suggested that the FDA can help improve patient awareness of the CV risk associated with diabetes (and often underappreciated complication) and spark discussions between patients and providers on this risk - and greater awareness of CV risk in turn could encourage lifestyle and other changes from patients. Further, she suggested that a diabetes drug indicated for the prevention of CV events could help health systems reorganize around a value-based framework. Ms. Close ultimately closed by thanking the FDA for its continued leadership in thinking in terms of outcomes beyond A1c for diabetes, including CV outcomes. See here for a full transcript of Ms. Close's remarks.
- **Florida Hospital's Dr. Richard Pratley spoke to both the robust design of the LEADER trial (as the co-chair of the global expert panel) and to how the results have influenced his own clinical practice.** Dr. Pratley described his role in the global expert panel, which was tasked which meeting regularly monitor the progress of the LEADER trial and ensure that all participants were treated to the best local standards by regularly providing feedback to clinic sites. Dr. Pratley attested to the fact that both CV risk factors and glycemia were well-treated in the study and that the trial enrolled a clinically-relevant population. Overall, Dr. Pratley expressed strong confidence in the validity of the results. Speaking on a more personal level, Dr. Pratley noted that, over the 30 years he has been in practice, diabetes prevalence has increased four-fold, but this sobering statistic has been accompanied by an explosion of new diabetes treatment options and an overall reduction in CV morbidity and mortality at the population level. Unfortunately, he pointed

out, improvements in CV risk in people with diabetes has not kept pace with the general population and patients with diabetes continue to face an enormous residual risk - a risk that we can now possibly address as we enter a "new era in diabetes management." Even without a label indication, Dr. Pratley described how he uses the results of the LEADER trial on a daily basis in his clinical practice to offer confidence that he is providing the best possible care for his patients.

- **Dr. Stephanie Fox-Rawlings of the National Center for Health Research (Vienna, VA) argued against an expanded indication for Victoza on the basis that the drug's cardioprotective effects were neither generalizable nor clinically relevant.** She did not dispute the validity of Victoza's statistically significant overall risk reduction for the primary outcome of three-point MACE, but took issue with the lack of statistical significance for this effect in the subgroup of participants living in the US (echoing the concerns of many panelists expressed earlier in the meeting's agenda). Since the FDA is a US agency, Dr. Fox-Rawlings contended, it needs evidence that Victoza reduces the risk of cardiovascular events in US patients. She furthermore highlighted that Victoza's overall cardioprotective effect, though impressive on a relative scale, translates to a vanishingly small absolute risk reduction - diminishing the incidence of cardiovascular events from 3.9 events per 100 patient years to only 3.4 events per 100 patient years. She argued that this absolute risk reduction is not sufficiently clinically relevant to warrant a label update for the drug - committee member Dr. Brendan Everett emphatically argued against this last point in his voting rationale at the end of the day.
- **Mr. Sammy Almashat (Public Citizen, Washington, DC) voiced strong opposition to a label update for Victoza,** calling it "not rational" to grant a new indication for US use when the geographical subgroup analysis didn't find statistically significant CV risk reduction for US-based participants. He also reminded the room that it would be atypical for the FDA to approve an indication based on a single trial (though that earlier precedent has already been shaken-up by the decision to update the Jardiance label according to EMPA-REG OUTCOME results alone). Both of Mr. Almashat's key points held some weight and were discussed in-depth by the voting panel, but we would find it truly disheartening if the geographical subgroup analysis invalidated what is otherwise incredibly compelling data. In fact, if a single large CVOT seems insufficient grounds for regulatory action, then a smaller subset of data from that same trial should definitely not be the deciding factor!
- **LEADER trial investigator and clinical endocrinologist Dr. Mark Warren discussed his confidence in the LEADER results and the paradigm-shift offered by the ability to impact CV risk alongside glucose.** As a member of the global expert committee, Dr. Warren is intimately familiar with how clinical care was standardized in the trial, lending him a high degree of confidence in the results that was only reinforced by the high rate of completion in the trial (only 29 patients were lost to follow-up). Speaking to the impact of the LEADER results on clinical practice, Dr. Warren underscored that his job as a clinician is to improve the lives of patients with diabetes, but until the EMPA-REG OUTCOME trial, there was no evidence to suggest which medications may improve CV risk. This was particularly troublesome for Dr. Warren, as he emphasized his preference for evidence-based clinical decision-making. He also underscored that diabetes is a metabolic disease that goes far beyond hyperglycemia - and now, for the first time, he can prescribe a diabetes drug that can also impact body weight and CV risk, with no increase in hypoglycemia. Speaking for the broader healthcare provider field, Dr. Warren suggested that inclusion of the LEADER data on the label for Victoza can help provide direction to providers as they treat their patients with high CV risk.
- **Dr. Robert Chilton (University of Texas, San Antonio, TX) emphasized the weight loss efficacy of liraglutide, explaining how important weight loss is to his patients.** In fact, he characterized the blood pressure-lowering, glucose-lowering, and reduced risk for CV events and particularly CV death as icing on the cake. He spoke from personal experience, describing how his patients feel low self-efficacy on insulin therapy due to the associated weight gain (not to mention hypoglycemia risk). He touched upon one of our favorite topics, the critical value of outcomes beyond A1c in diabetes care, in his closing words: "It's not just about glucose anymore."

- **Dr. Mansur Shomali (MedStar Union Memorial Hospital, Baltimore, MD) suggested that the LEADER results offer him confidence in his clinical decisions for patients with diabetes at high risk for CV events.** Dr. Shomali described how many of his patients with type 2 diabetes struggle with cardiovascular disease as well. Speaking to a specific patient who was recently discharged after a stroke, Dr. Shomali shared how he felt for the first time that he would actually be helping this patient (rather than just treating numbers and lowering A1c) by prescribing Victoza. Furthermore, Dr. Shomali highlighted that this reduction in CV risk is accompanied by assurance of a low risk of hypoglycemia, modest weight loss, and modest blood pressure reduction. Looking to a different patient of his who recently underwent surgery for a CV event, Dr. Shomali underscored the benefits of Victoza over basal-bolus therapy for post-CV event patients with diabetes, as it lowers glucose without hypoglycemia (a risk factor for future CV events) and likely confers a cardioprotective benefit as well. What's more, Victoza therapy is a once-daily injection and is far less complex that the four daily injections associated with basal-bolus therapy. Safe and effective, Victoza thus has the potential to promote longevity and improve quality of life, all while potentially reducing daily treatment burden. A favorable vote from the Advisory Committee, Dr. Shomali argued, has the potential to highlight these favorable CV risk benefits and, as he put it, allow providers to "have confidence in using a drug that has been shown to be safe and potentially beneficial in people with high CV risk."
- **Mr. Vincent Coles addressed the panel with a deeply personal account of his experience as a participant in the Victoza arm of the LEADER trial.** He eloquently described his initial reticence to enroll in the study due to the daunting time commitment (four to five years) and because of a persistent fear of needles. Despite this, Mr. Coles entered the study at the recommendation of his primary care doctor and his wife, who assisted him with the Victoza injections every night. He quickly saw the benefit of the study drug, watching his A1c fall from 9% to 7% and losing 20 pounds over the course of the study. Remarking on his family's strong history of cardiovascular events, Mr. Coles explained his deep felt concerns over his cardiovascular health and the importance of minimizing his risk by all means possible. "If asked if I benefitted from the LEADER trial I would say yes, and if asked if I would take Victoza again I would say yes - but hopefully soon in oral form!" he surmised.
- **AACE President Dr. Jonathan Leffert showed how the LEADER trial is already changing diabetes management for the better, since the AACE treatment algorithm already top-lists GLP-1 agonists.** He qualified that AACE does not advocate for approval of any specific product, nor does it petition for specific label claims. But at its core, the organization aims to spread tools for highest-quality care - in this case, Dr. Leffert stated emphatically, a new CV indication for Victoza is an important tool for healthcare providers treating diabetes and working to manage CV complications. Moreover, he argued that patients with type 2 diabetes only stand to benefit from the proposed indication. Dr. Leffert reviewed CVOT data for other GLP-1 agonist agents, including lixisenatide (Sanofi's Lyxumia) and exenatide once-weekly (AZ's Bydureon), both of which showed neutral effects on three-point MACE. It's looking more and more like cardioprotection may not be a class effect for GLP-1 agonists, but is rather inherent to certain molecules within the class. This means that recognizing CV benefit where it exists is crucial, so that patients/providers have easy access to all the available scientific knowledge and are empowered to approach best practice diabetes care.
- **ADA VP of Research Programs Dr. Tamara Darsow emphasized the huge unmet residual CV risk present in people with diabetes and the opportunity represented by diabetes drugs that can positively impact this residual risk.** She underscored that cardiovascular disease remains the major cause of death in patients with diabetes, despite significant advances in glycemic and CV risk management. She also highlighted that one in five US healthcare dollars are spent on diabetes - and much of this cost is driven by CV morbidity and mortality. Historically, diabetes and CV risk factors have been managed separately and with a combination of therapies - and yet too few patients are able to achieve targets for A1c, blood

pressure, and lipids simultaneously. In this context, Dr. Darsow emphasized the critical importance of communicating to providers information about diabetes drugs that can actually have a favorable effect on CV disease, even on top of optimized treatment. In closing, she made a powerful statement to generate a sense of urgency behind a Victoza label update: "The enormous burden of CV disease in people with diabetes requires that these medications can be recommended to the patients that need them the most."

- **On behalf of the diabetes market research company dQ&A, our very own Ms. Abigail Dove (Close Concerns, San Francisco, CA) spoke to the potential of a CV indication for Victoza to offer patients much-needed hope to patients in an era of widespread frustration about diabetes care.** Drawing upon data from a recent dQ&A survey of nearly 3,500 people with diabetes, Ms. Dove pointed out that people's perceptions of their current diabetes therapies are strikingly negative: among people with type 2 diabetes, less than a third of respondents - 29% - indicated their current diabetes care regime was "very successful," and an even lower 23% indicated their current diabetes care regime as being "very successful" at fostering freedom from worry about their long-term health outlook. Ms. Dove remarked that people with diabetes are bombarded with fearful messaging about the urgency of managing their diabetes to prevent the sequaela of complications like cardiovascular disease, often from the moment of diagnosis. However, the findings from dQ&A demonstrate that patients have little confidence in their current diabetes therapies to deliver on precisely this. She argued that a great deal of hope could be inspired in people with diabetes if Victoza's indication were updated to reflect its ability to reduce cardiovascular events in high-risk patients, by empowering them with the knowledge that they have one more tool in the fight against diabetes and its complications, and it is possible to live long and live well with diabetes. See Ms. Dove's full remarks here.
- **Speaking as a future physician, our own Ms. Helen Gao discussed the value of a CV indication for Victoza in educating busy healthcare providers about the significant and clinically meaningful benefits demonstrated in the LEADER trial.** She emphasized her own surprise and disappointment that the LEADER results did not make front page headlines in the mainstream press and highlighted the challenges many healthcare providers face in attempting to stay current with the wealth of new data out of diabetes cardiovascular outcomes trials (CVOTs) and other studies, particularly as providers face increasing time pressures in the changing healthcare system. Ms. Gao drew on data from diabetes market research firm dQ&A to show that, in a survey of diabetes educators, 81% of respondents were not familiar with the LEADER trial and results and only 3% were "very familiar with the results." Furthermore, she underscored that knowledge about the LEADER results would likely have a meaningful impact on clinical decision-making. In the same survey, only 16% of respondents said that the LEADER results would have no impact on their clinical recommendations for patients at high risk for CV events. On the other hand, 45% of respondents said that the LEADER results would make them more likely to recommend Victoza over other GLP-1 agonists for patients at high risk for CV events. In addition, 42% of respondents said that they were more likely to recommend any GLP-1 agonist as a second-line therapy following metformin for these high-risk patients after learning of the results. Ms. Gao especially emphasized the importance of this last finding - GLP-1 agonists are still vastly under used in diabetes care (as evidenced by the recent finding that only 5% of US diabetes patients were taking a GLP-1 agonist in 2013). This is particularly disappointing in the context of the demonstrated A1c, weight loss, hypoglycemia, and CV benefits of these agents. Overall, Ms. Gao urged the committee to consider voting in favor of an updated label indication in order to make it easier for providers to practice evidence-based medicine and improve adoption of these advanced agents. See here for a full transcript of her remarks.
- **Close Concerns' own Ms. Payal Marathe shared insights gathered from scientific meetings and diabetes thought leaders, all favoring approval of the new CV indication.** Subsequent analyses of the LEADER trial, following presentation of full results to an overflowing conference hall at ADA 2016, have supported liraglutide's robust CV benefit. Just recently at ADA

2017, we learned that the CV data consistently favors liraglutide over placebo, even when controlling for potential intermediate factors like concomitant medications, recurrent CV events, and episodes of severe hypoglycemia. Experts are leaning toward anti-atherosclerotic effects as the cardioprotective mechanism underlying liraglutide, but mechanism aside, the consensus among thought leaders is certainly that this outcomes data is compelling and should be used to save as many lives as possible. It is a missed opportunity - if not unacceptable - to keep information of a 13% risk reduction for major CV events tucked away, when so many patients could benefit from liraglutide's CV effects displayed clearly on a product label. For the full text of her remarks, click here.

Commentary from Voting Members

Following the final panel vote, each panelist was given a few minutes to explain his or her decision. Included below are summaries of each statement for the voting question of whether LEADER provides substantial evidence of cardiovascular risk reduction. The comments are split by "yes" and "no" votes and arranged in alphabetical order by speakers' last names. The panel vote was resoundingly - but not unanimously - in favor of approval of an additional indication for cardiovascular benefit, with 17 members voting in favor and 2 voting against. Several of the "yes" votes expressed concerns and caveats as well. The other voting question of whether the LEADER results met the bar to demonstrate cardiovascular safety for liraglutide was met with a unanimous "yes" vote.

Yes

- **Cardiologist Dr. Michael Blaha (John Hopkins University, Baltimore, MD) voted "yes," on the proposed CV efficacy indication for Victoza, noting that the LEADER results clearly show that people with diabetes and high CV risk will benefit from Victoza.** He praised the LEADER trial for meeting or trending toward significance on all of the measured cardiovascular endpoints - a rarity compared to other CVOTs in which these individual components tend not to move in lockstep. Dr. Blaha also mentioned that the US subgroup analysis gave him a certain degree of pause, but closed with the notion that subgroups are small and can be over-interpreted. Like all panelists, he voted "yes" on the question of whether the LEADER trial had successfully established cardiovascular safety.
- **Endocrinologist Dr. Kenneth Burman (MedStar Washington Hospital Center, Washington, DC) voted yes on the basis of liraglutide's impressive 13% overall risk reduction for the primary outcome of three-point MACE, also noting the need for anti-diabetic agents that are likely to improve cardiovascular risk.** He noted that this was a "difficult decision," expressing concerns about the unknown mechanism of liraglutide's cardioprotective effects and the lack of statistical significance for the individual endpoints of non-fatal MI, non-fatal stroke, and heart failure (though these all trended toward significance and had point estimates <1). His "yes" vote on the question of whether the LEADER trial had successfully established cardiovascular safety was unequivocal.
- **Cleveland Clinic's Dr. Leslie Cho voted yes, but reiterated concerns regarding the discrepancy between study population and requested indication.** She admitted being "troubled" by the request for a broader indication of high CV risk when LEADER data was most compelling for type 2 diabetes patients with established CV disease at baseline. In other words, Dr. Cho - like a few others on this Advisory Committee - was troubled by the inclusion criteria subgroup analysis and the nonsignificant risk reduction shown for cohort 3b. We hope that no single subgroup analysis discolors the overall positive finding from LEADER, but we definitely recognize the possibility that the FDA may tweak the requested indication before approving it (perhaps using more stringent language for the implicated patient population). Of note, Dr. Cho was one of the strongest-in-favor yes votes at the Jardiance Advisory Committee meeting last year. She also voted yes for liraglutide's demonstrated CV safety vs. placebo.

- **Dr. Brendan Everett (Brigham and Women's Hospital, Boston, MA) contributed a strong "yes" vote in favor of an updated indication.** He characterized the existence of a diabetes drug with important benefits on CV endpoints (particularly CV mortality) as a "huge breakthrough for patients and clinicians alike." Overall, he felt that the LEADER trial was well-conducted. He was particularly convinced by the results for CV and all-cause mortality, though he also found the consistency of effect across all endpoints compelling. He also emphasized that the absolute risk reduction - while it may sound small to some - is substantial and clinically meaningful, especially in the context of years and years during which diabetes drugs had zero demonstrate benefit on CV absolute risk reduction. In terms of the appropriate population for the indication, Dr. Everett advocated for the use of Victoza in those with clinical cardiovascular disease or those with subclinical disease (like non-obstructive coronary disease and perhaps chronic kidney disease). The aspect of the trial and vote that Dr. Everett struggled the most with was whether or not the single LEADER trial was sufficient to support a CV indication - ultimately, Dr. Everett recalled his deliberations from the Jardiance discussion a year ago and voted in a manner that is "intellectually consistent" with his positive vote in favor of the Jardiance indication. Regarding the first CV safety voting question, Dr. Everett voted "yes," noting that LEADER was well-conduced and convincingly excluded the hazard ratio point estimate of 1.3 designating unacceptable risk.
- **Dr. Judith Fradkin (NIDDK, Bethesda, MD) voted in favor of an indication of CV efficacy in the high-risk population that was studied in LEADER.** While she suggested that liraglutide might confer some CV benefit to people at lower-risk for CV morbidity/mortality as well, she maintained that any new indication granted should be based solely on what the LEADER trial demonstrates. On voting question no. 1, regarding the CV safety of liraglutide vs. placebo, Dr. Fradkin was strongly in support.
- **Consumer representative Ms. Diana Hallare (Visalia, CA) voted in favor of a CV indication for Victoza, though she emphasized that the benefit appears to mainly apply to those with established cardiovascular or renal disease.** Regarding the US subgroup issue, Ms. Hallare expressed concerns about the study duration in the US population compared to that in Asia and Europe. She also noted that she'd like to see the CV impact of different dosages of Victoza compared - in the trial, investigators were encouraged to up titrate participants to the highest 1.8 mg dose as long as they could tolerate it, leading to a higher proportion of participants on the 1.8 mg dose compared to the actual US diabetes population taking Victoza. Other than these concerns, however, Ms. Hallare emphasized that LEADER produced convincing outcomes, particularly with the primary endpoint. Ms. Hallare's "yes" vote was a big win, considering that she voted against an expanded indication for Jardiance last year, citing concerns over the high proportion of undetermined deaths and the controversy over how silent MI was counted in the EMPA-REG OUTCOME trial. Ms. Hallare's vote today further underscores the strong design and execution of the LEADER trial. Ms. Hallare also voted "yes" to the question of whether Victoza sufficiently demonstrated CV safety, citing both the overall MACE finding as well as the positive reductions in CV risk factors like systolic blood pressure and cholesterol.
- **Dr. James de Lemos (University of Texas Southwestern Medical Center, Dallas, TX) voted yes, remarking that the LEADER trial's primary endpoint result was borderline in his eyes, but buoyed by strong results for the individual outcomes of CV death and all-cause mortality.** Notably, Dr. de Lemos also voted for a cardiovascular indication for Jardiance in last year's EMDAC meeting, again swayed by the robustness of the CV death and all-cause mortality findings from the EMPA-REG OUTCOME trial. He additionally voted an enthusiastic "yes" on the question of whether the LEADER trial had successfully established cardiovascular safety.
- **Endocrinologist Dr. Cecilia Low Wang (University of Colorado, Aurora, CO) voted "yes," noting that she found the LEADER trial's primary endpoint results very convincing.** She shared the concerns of several panelists regarding the lack of statistical significance on this outcome for the US subgroup of LEADER participants, but noted that this could

be convincingly explained by reduced drug adherence in US versus non-US patients. To our delight, Dr. Low Wang additionally highlighted how the LEADER trial data illustrates the important heterogeneity among people with type 2 diabetes by demonstrating that there is a wide continuum of how cardiovascular risk can manifest itself (and accordingly, which drugs are most effective for which aspects of cardiovascular risk). She additionally voted "yes" on the question of whether the LEADER trial had successfully established cardiovascular safety.

- **Dr. Marvin Konstam (Tufts University, Boston, MA) was a firm yes vote, despite reservations related to the US subgroup.** "At the end of the day, I can't overrate that to diminish the overall finding," he explained during his voting rationale. What did compel him about the LEADER results was the significant 22% risk reduction for CV mortality, which he called the "biggest contributor" to the positive primary endpoint finding. Dr. Konstam seemed very much on the fence at the Jardiance Advisory Committee last year, though he ultimately voted in favor of that CV indication as well. He was also a firm yes on voting question no. 1 for liraglutide, endorsing its CV non-inferiority vs. placebo.
- **Patient representative Ms. Debra McCall (who made her debut on an endocrinology Advisory Committee, following several appearances on cardiology committees) voted strongly, passionately yes.** She described how obesity, type 2 diabetes, and CV disease run in her family - in her view and personal experience, these three conditions are inextricably linked and should be approached as such by the healthcare system. Ms. McCall argued that a weight-lowering, cardioprotective therapy like liraglutide is a tool providers need in their arsenal. She expressed how truly disappointed she would be if CV benefit remained absent from the product label, given how convincing the LEADER results are and how essential cardioprotective therapies are for people living with diabetes and obesity. Ms. McCall voted yes for liraglutide's CV safety vs. placebo as well.
- **Dr. James Neaton (University of Minnesota, Minneapolis, MN) contributed a strong vote in favor of an updated indication for Victoza.** All in all, Dr. Neaton cited the CV mortality benefit in the overall population as particularly convincing and the major driver behind his vote. In addition, he cited the consistency of the CV results in the trial as a substantial influence on his vote as well. While acknowledging that there may be some nuance in the target population of benefit that needs to be worked out for the indication language, Dr. Neaton pointed out that the overall event rate across the trial was twice as high as was expected, indicating that the participant population overall was clearly very high risk compared to the general population. Dr. Neaton also voted "yes" for the question of whether Victoza adequately addressed the CV safety requirement set forth by the FDA. Dr. Neaton previously contributed a strong positive vote in favor of a CV mortality indication for Jardiance.
- **Speaking through the phone, Dr. David Oakes (University of Rochester, NY) voted yes and echoed many of the sentiments voiced by other committee members.** He mentioned minor concerns regarding the geographical subgroup analysis, and suggested that this be addressed in how the indication is worded. Indeed, we'll be very curious to see if/how the FDA tweaks Novo Nordisk's proposed indication (though the most likely change, we anticipate, would be to clarify the implicated patient population in terms of primary vs. secondary CV prevention). Dr. Oakes voted yes for liraglutide's CV safety vs. placebo on voting question no. 1.
- **Dr. David Robbins (University of Kansas, Kansas City, KS) voted "yes" based on the strength of the primary outcome for three-point MACE.** While he also echoed previous panelists' concerns regarding the lack of statistical significance for this outcome in the US subgroup versus the non-US subgroup, Dr. Robbins ultimately felt that the issue was not black and white, and that the strong risk reduction for cardiovascular events with Victoza in the overall population outweighed this subgroup issue. Very notably, he closed his commentary with a nod toward the outcomes beyond A1c movement, underscoring the need for diabetes treatments that offer benefits beyond lowering blood glucose. Dr. Robbins also voted "yes" on the question of whether the LEADER trial had successfully established cardiovascular safety.

- **Cardiologist Dr. Yves Rosenberg (NIH, Bethesda, MD) voted yes on the basis of the LEADER trial's compelling consistency across all cardiovascular outcomes measured.** However he noted that the issue of a cardioprotective benefit for liraglutide is "more complicated" from a clinical point of view than a statistical one because of the LEADER trial's arguably small absolute risk reduction for cardiovascular events, Dr. Rosenberg maintained that "this shouldn't prevent the approval of this indication" - especially in light of the fact that a cardiovascular indication for Jardiance was approved on the basis of arguably less statistically powerful data in the EMPA-REG OUTCOME. (Indeed, Dr. Rosenberg voted against a label update for Jardiance in last year's EMDAC meeting). He issued an unreserved "yes" on the question of whether the LEADER trial had successfully established cardiovascular safety.
- **Distinguished oncologist Dr. Hanna Sanoff (University of North Carolina, Chapel Hill, NC) noted that the hazard ratio for the LEADER trial's primary outcome is "unequivocally in favor of the drug reducing cardiovascular events," but noted that her "yes" vote is clouded by some skepticism of the clinical relevance of this risk reduction.** Though liraglutide boasts an impressive 13% absolute risk reduction in three-point MACE compared to placebo, the relative benefit of this against the backdrop of an already fractional risk of having a cardiovascular event in the first place is much less dramatic. Said another way, liraglutide impressively reduces the risk of cardiovascular events, but is less impressive at reducing the actual number of cardiovascular events that occur because this happens from a low base (though albeit a much higher base than the general, non-diabetes population). Dr. Sanoff additionally expressed concerns about the generalizability of the LEADER trial data to the US population, given the lack of statistical significance for the primary endpoint in the US subgroup. Her answer was a clear "yes" on the question of whether the LEADER trial had successfully established cardiovascular safety.
- **Chairperson Dr. Peter Wilson (Emory University, Atlanta, GA) voted "yes" for an updated label reflecting CV benefit for Victoza, though he expressed some uncertainty in terms of the appropriate patient population for the indication.** He pointed out that the subgroups of CV risk employed in the trial's enrollment criteria do not perfectly match up with more traditional definitions of "primary" and "secondary" prevention (previous history of CV events vs. risk factors only, respectively). Ultimately, Dr. Wilson found Dr. Konstam's proposed target population compelling: people with atherosclerotic disease and its subclinical manifestations. Dr. Wilson further expressed his hope that this in the patient population that will have access to this drug. Regarding the safety voting question, Dr. Wilson gave a strong yes vote, noting that upper bounds for all of the confidence intervals for every CV endpoint in every subgroup were not even close to reaching the 1.3 threshold for unacceptable risk specified in the FDA's 2008 CVOT policy. As chairperson of the committee and a negative vote for the Jardiance label last year, Dr. Wilson's positive vote is particularly notable and a huge win.
- **Dr. Susan Yanovski (NIDDK, Bethesda, MD) provided another vote in favor of the indication, characterizing the reductions in MACE, CV mortality, and all-cause mortality demonstrated in the trial as both statistically significant and clinically meaningful.** In terms of the indicated population, Dr. Yanovski found the benefit compelling in people with established cardiovascular disease and others in the highest risk group in the trial. On the other hand, she was less convinced of a benefit in the "lower-risk" subgroup enrolled in the trial. Overall, she left it up the FDA to determine the exact language for population of benefit in the indication. Dr. Yanovski also voted in favor of the first safety voting question.

No

- **The CDC's Dr. Daniel Budnitz issued the first "no" vote, underscoring that he felt it inappropriate to favor a cardiovascular indication for Victoza from the US FDA when the US subgroup of the LEADER trial showed no statistical cardiovascular benefit with the drug.** He additionally expressed concern that it is a "slippery slope" to make decisions about

label updates on the basis of a single clinical trial. Notably Dr. Budnitz also voted against a label update for Jardiance in last year's EMDAC meeting on the EMPA-REG OUTCOME data. That said, he issued an unreserved "yes" on the question of whether the LEADER trial had successfully established cardiovascular safety.

- **Oncologist Dr. Carmen Allegra (University of Florida, Gainesville, FL) voted "no" also on the basis of concerns about the lack of a statistically significant cardiovascular benefit for Victoza in the US subgroup.** He noted that it is important to further investigate the reason underlying this anomaly in the US subgroup, whether it is attributable to lack of exposure to liraglutide, adherence challenges, different underlying clinical practices, a combination of these forces, or something entirely different. That said, Dr. Allegra issued a clear "yes" on the question of whether the LEADER trial had successfully established cardiovascular safety.

-- by Ann Carracher, Abigail Dove, Helen Gao, Payal Marathe, and Kelly Close